Published in final edited form as:
Int J Cardiol. 2014 March 15; 172(2): e285–e287. doi:10.1016/j.ijcard.2013.12.200.

Association of soy food intake with risk and biomarkers of coronary heart disease in Chinese men

Danxia Yu[a], **Xianglan Zhang**[a,*,1], **Yong-Bing Xiang**[c], **Gong Yang**[a], **Honglan Li**[c], **Sergio Fazio**[b], **MacRae Linton**[b], **Qiuyin Cai**[a], **Wei Zheng**[a], **Yu-Tang Gao**[c], and **Xiao-Ou Shu**[a,1]

[a]Division of Epidemiology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA

[b]Division of Cardiovascular Medicine, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA

[c]Department of Epidemiology, Shanghai Cancer Institute, Shanghai, China

Keywords

Soy foods; Coronary heart disease; Men; Prospective cohort study; Interleukin-8; Plasminogen activator inhibitor-1

Soy food intake has been associated with a reduced risk of coronary heart disease (CHD) in women, but its association with CHD in men is unclear [1–3]. Several studies have found sex differences in the associations of soy intake with metabolic syndrome, endothelial function, and other cardiovascular risk factors [4,5]. In the Shanghai Men's Health Study [6], we investigated the association between soy food intake and incident CHD among 55,474 Chinese men (40–74 years) who were free of CHD, stroke, and cancer at baseline (2002–2006). We also examined the associations of soy intake with multiple CHD biomarkers in a subsample of 3,885 men who provided fasting blood samples and had no history of major chronic diseases at recruitment.

Usual dietary intakes were assessed through in-person interviews using a validated food-frequency questionnaire [6]. Energy and nutrient intakes, including soy protein and isoflavones, were calculated based on 2002 Chinese Food Composition Table. Participants who reported extreme energy intake (<800 or >4,200 kcal/day) were excluded from analysis. Dietary intakes were adjusted for total energy by using the residual method. Incident CHD

*Corresponding author at: Vanderbilt Epidemiology Center, Institute for Medicine and Public Health, 2525 West End Avenue, Suite 600, Nashville, TN, 37203-1738. Tel: +1 615 936 0956, fax: +1 615 936 8291. xianglan.zhang@vanderbilt.edu (Xianglan Zhang).
[1]This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

The authors' contributions were as follows: XZ, Y-BX, GY, WZ, Y-TG and X-OS designed research cohort; XZ, Y-BX, GY, HL, ML, QC, WZ, Y-TG and X-OS contributed to study implementation and data collection; DY, XZ, GY, SF, WZ and X-OS analyzed and interpreted data; DY drafted the manuscript. All authors contributed to the revision of the manuscript, read and approved the final manuscript.

None of the authors had any conflicts of interest to declare.

Conflicts of interest: None reported.

cases (nonfatal myocardial infarction and fatal CHD) were ascertained via follow-up home visits (follow-up rate: 94%) and linkage to the Shanghai Vital Statistics Registry (>99% complete). The diagnosis of cases was further confirmed by reviewing medical records and/or death certificates. Hazard ratios of CHD and 95% confidence intervals were estimated using Cox regression with age as the timescale. Measurements of plasma biomarkers have been described previously and shown reasonable intra-assay and intra-person coefficients of variation [7]. Multivariable-adjusted geometric means of biomarkers by soy protein intake were calculated and compared using linear regression. Written informed consent was obtained from each participant. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institutional review boards of all participating institutes.

The median soy protein intake was 9.5 g/day (interquartile range: 6.3–13.7 g/day). During a mean follow-up of 5.4 years, we identified and validated 217 incident CHD cases. Soy intake showed a positive, independent, and dose-response association with risk of CHD. After adjustment for several CHD risk factors and other dietary intakes (Table), the hazard ratios were 1 (referent), 1.23, 1.47, and 1.58 (95% confidence interval: 1.06–2.36) from the lowest to highest quartile of soy protein intake (*P* for trend =0.02). Restricted cubic spline analysis revealed that CHD risk increased gradually with increasing soy protein intake up to ~15 g/day (80^{th} percentile); the increase in risk flattened off thereafter (Figure). Positive associations persisted in analyses confined to men without diabetes and family history of cardiovascular diseases and men had no or little change in soy intake in last 5 years. No effect modifications were found for obesity, physical activity, smoking, alcohol consumption, hypertension, soy intake during adolescence, and other dietary factors. Results did not change when the first year of follow-up was excluded. Similar positive associations were observed for soy isoflavones and total soy food consumption.

In cross-sectional analysis of biomarkers, soy intake was significantly associated with higher plasma concentrations of interleukin-8 (IL-8) and plasminogen activator inhibitor-1 (PAI-1). In the lowest and highest quartiles of soy protein intake, the multivariable-adjusted geometric means were 1.4 and 1.6 pg/ml for IL-8 and 17.6 and 18.9 ng/ml for PAI-1 (both *P* for trend <0.01). We did not find significant associations of soy intake with other biomarkers, including blood lipids, glucose, insulin, C-reactive protein, and adipokines.

Few epidemiological studies, mainly from Asian populations, have investigated the relationship between soy food intake and incident CHD. A potential cardioprotective effect of soy foods has been reported in Chinese and Japanese women [1–3]. To our knowledge, our study is the first to focus on soy foods and risk of CHD in men and provide the evidence that habitual high soy intake may have adverse effects on the development of CHD in men.

The mechanisms behind the possible adverse effects of high soy intake on cardiometabolic health in men are largely unknown. Elevated IL-8 and PAI-1 are markers of impaired vascular endothelium and hypercoagulable states. The positive associations of soy intake with these biomarkers observed in our study might provide some explanations. Previous studies have suggested sex-specific associations of soy foods with cardiometabolic health, with favorable associations observed in women and unfavorable associations in men [4,5]. Clinical trials to date overall found no influence of soy protein or isoflavones on endothelial function [8]. Some studies, nevertheless, did observe male-specific adverse effects of soy-supplemented diet on coagulation and fibrinolysis [5,9]. It is also possible that other mechanisms, e.g. sex hormonal pathways, or other components of soy products or metabolites, e.g. trimethylamine-N-oxide, a metabolite from soy lecithin by gut microbiota [10], may be responsible for the observed adverse associations in men.

Major concerns of our study include potential dietary measurement errors and residual confounding. However, because of the prospective design, exposure misclassification is likely to be non-differential and result in an underestimation of the association. Although we cannot rule out the presence of residual confounding, we have adjusted for a range of potential confounders and found similar associations with and without multivariable adjustment.

In conclusion, habitual high soy food intake may be associated with increased risk of incident CHD in middle-aged and older Chinese men; elevated plasma IL-8 and PAI-1 might be potential contributing factors.

Acknowledgments

Grants support: R01HL079123, R01HL095931, and R01CA082729 from the US National Institutes of Health. The funding sources were not involved in the data collection, data analysis, manuscript writing, and publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Zhang X, Shu XO, Gao YT, et al. Soy food consumption is associated with lower risk of coronary heart disease in Chinese women. J Nutr. 2003; 133:2874–8. [PubMed: 12949380]
2. Zhang X, Gao YT, Yang G, et al. Urinary isoflavonoids and risk of coronary heart disease. Int J Epidemiol. 2012; 41:1367–75. [PubMed: 22927214]
3. Kokubo Y, Iso H, Ishihara J, Okada K, Inoue M, Tsugane S. Association of dietary intake of soy, beans, and isoflavones with risk of cerebral and myocardial infarctions in Japanese populations: the Japan Public Health Center-based (JPHC) study cohort I. Circulation. 2007; 116:2553–62. [PubMed: 18025534]
4. Pan A, Franco OH, Ye J, et al. Soy protein intake has sex-specific effects on the risk of metabolic syndrome in middle-aged and elderly Chinese. J Nutr. 2008; 138:2413–21. [PubMed: 19022966]
5. Teede HJ, Dalais FS, Kotsopoulos D, Liang YL, Davis S, McGrath BP. Dietary soy has both beneficial and potentially adverse cardiovascular effects: a placebo-controlled study in men and postmenopausal women. J Clin Endocrinol Metab. 2001; 86:3053–60. [PubMed: 11443167]
6. Cai H, Zheng W, Xiang YB, et al. Dietary patterns and their correlates among middle-aged and elderly Chinese men: a report from the Shanghai Men's Health Study. Br J Nutr. 2007; 98:1006–13. [PubMed: 17524168]
7. Lee SA, Kallianpur A, Xiang YB, et al. Intra-individual variation of plasma adipokine levels and utility of single measurement of these biomarkers in population-based studies. Cancer Epidemiol Biomarkers Prev. 2007; 16:2464–70. [PubMed: 18006938]
8. Beavers DP, Beavers KM, Miller M, Stamey J, Messina MJ. Exposure to isoflavone-containing soy products and endothelial function: a Bayesian meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis. 2012; 22:182–91. [PubMed: 20709515]
9. Stauffer BL, Konhilas JP, Luczak ED, Leinwand LA. Soy diet worsens heart disease in mice. J Clin Invest. 2006; 116:209–16. [PubMed: 16395406]
10. Wang Z, Klipfell E, Bennett BJ, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011; 472:57–63. [PubMed: 21475195]

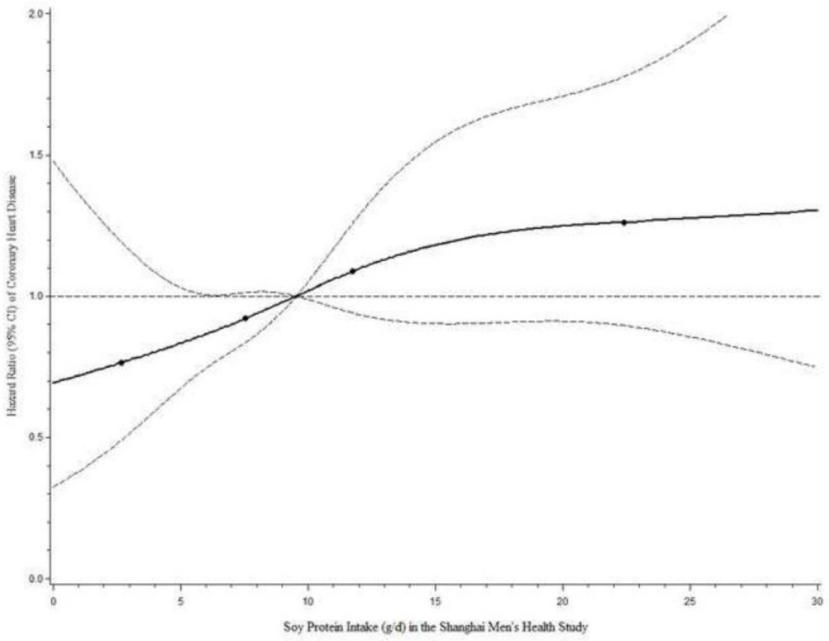

Figure.

Risk of coronary heart disease by soy protein intake in the Shanghai Men's Health Study (— hazard ratio, ---- 95% confidence interval)[a]

[a] Four knots: 5th, 35th, 65th and 95th percentiles. Referent: median intake 9.5 g/day. Model was adjusted for all variables listed in the footnote of Table Model 2.

Table

Hazard ratio (95% confidence interval) of coronary heart disease by soy food intake in the Shanghai Men's Health Study (n= 55,474)

	Quartiles of soy food intake				*P* for trend
	1	**2**	**3**	**4**	
Soy protein					
Median, g/day	4.3	7.9	11.3	17.3	
No. of cases	42	48	60	67	
Age- and energy- adjusted model	1.00	1.15 (0.76, 1.74)	1.37 (0.92, 2.03)	1.48 (1.01, 2.18)	0.03
Model 1	1.00	1.22 (0.81, 1.85)	1.45 (0.98, 2.16)	1.55 (1.05, 2.30)	0.02
Model 2	1.00	1.23 (0.81, 1.87)	1.47 (0.99, 2.20)	1.58 (1.06, 2.36)	0.02
Isoflavones					
Median, mg/day	13.5	25.5	37.6	58.3	
No. of cases	44	43	66	64	
Age- and energy- adjusted model	1.00	0.99 (0.65, 1.50)	1.46 (1.00, 2.14)	1.34 (0.92, 1.97)	0.06
Model 1	1.00	1.04 (0.68, 1.59)	1.57 (1.07, 2.30)	1.40 (0.95, 2.07)	0.04
Model 2	1.00	1.04 (0.68, 1.59)	1.58 (1.07, 2.33)	1.42 (0.96, 2.11)	0.04
Soy foods (dry weight)					
Median, g/day	11.3	19.6	27.5	41.1	
No. of cases	48	41	58	70	
Age- and energy- adjusted model	1.00	0.84 (0.55, 1.28)	1.13 (0.77, 1.66)	1.31 (0.91, 1.90)	0.05
Model 1	1.00	0.90 (0.59, 1.36)	1.23 (0.84, 1.81)	1.40 (0.96, 2.03)	0.03
Model 2	1.00	0.91 (0.60, 1.38)	1.25 (0.84, 1.84)	1.43 (0.98, 2.10)	0.02

Model 1: adjusted for age, income, education, physical activity, smoking, alcohol consumption, body mass index, waist-to-hip ratio, use of vitamin E, multivitamin supplement, aspirin, family history of cardiovascular disease, history of hypertension or diabetes, and total energy intake. Model 2: further adjusted for dietary intakes of fruit, fish, red meat, saturated fat and sodium.